FILE 'REGISTRY' ENTERED AT 15:09:57 ON 26 JUL 1999
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DICTIONARY FILE UPDATES: 25 JUL 99 HIGHEST RN 228878-07-7

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Please note that search-term pricing does apply when conducting SmartSELECT searches.

=> d 18 que stat;d 1-2 ide cbib abs

SRIPADA
214984

=> s (tumour or tumor or vinca alkaloid? or fluorouracil or cisplatin or taxol or antibiotic?) and (propargyl(1)deaza(1)amino(1)pterine or 14)

COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID
The query entered contains both search terms created by structure-building or screen commands and text search terms. L#s created via the STRUCTURE or SCREEN commands must be searched in the structures files separately from text terms or profiles. The L# answer sets from structure searches can be used in crossover searches and can be combined with text terms.

=> s (tumour or tumor or vinca alkaloid? or fluorouracil or cisplatin or taxol or antibiotic?) and (propargyl(1)deaza(1)amino(1)pterine or 1110)

L11 0 FILE MEDLINE
L12 0 FILE HCAPLUS
L13 0 FILE BIOSIS
L14 0 FILE EMBASE
L15 0 FILE WPIDS

TOTAL FOR ALL FILES
L16 0 (TUMOUR OR TUMOR OR VINCA ALKALOID? OR FLUOROURACIL OR CISPLATIN
OR TAXOL OR ANTIBIOTIC?) AND (PROPARGYL(L) DEAZA(L) AMINO(L) PTERINE OR LL10)

=> dis his

I.; Colwell, William T.; Sirotnak, Francis M.; Smith, R. Lane; Piper, James R. (SRI International, USA). U.S. US 5354751 A 19941011, 24 pp. Cont.-in-part of U.S. Ser. No. 28,431. (English). CODEN: USXXAM. APPLICATION: US 1993-90750 19930712. PRIORITY: US 1992-845407 19920303; US 1992-875779 19920429; US 1992-938105 19920831; US 1993-8919 19930126; US 1993-28431 19930309.

REFERENCE 4: 122:160688 Process for preparing 10-deazaaminopterins and 5,10-
and 8,10-dideazaaminopterins from pteroate diesters. DeGraw, Joseph I.; Colwell, William T.; Piper, James R. (USA). U.S. US 5374726 A 19941220, 19 pp. Cont.-in-part of U.S. Ser. No. 845-407, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1993-28431 19930309. PRIORITY: US 1992-845407 19920303; US 1992-875779 19920429; US 1992-938105 19920831; US
1993-8919 19930126.

REFERENCE 5: 120:245139 Process for preparing 10-deazaaminopterins and 5,10-
and 8,10-dideazaaminopterins from pteroic dicarboxylic acid diesters. Degraw, Joseph I.; Colwell, William T.; Piper, James R. (SRI International, USA). PCT Int. Appl. WO 9322316 A1 19931111, 41 pp. DESIGNATED STATES: W: AU, CA, JP, KR; RW: AT, BE, CH, DE, DK, ES, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US3966 19930428. PRIORITY: US 1992-875779 19920429; US 1992-938105 19920831; US 1993-8919 19930126; US 1993-28431 19930309.

REFERENCE 6: 119:72415 Synthesis and antitumor activity of 10-propargyl-10-deazaaminopterin. DeGraw, Joseph I.; Colwell, William T.;
Piper, James R.; Sirotnak, Francis M. (Bio-Org. Chem. Lab., SRI Int., Menlo Park, CA, 94025, USA). J. Med. Chem., 36(15), 2228-31 (English) 1993. CODEN: JMCMAR. ISSN: 0022-2623.

=> fil medl,hcaplus,biosis,embase,wpids

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 269.91 | 2555.55 |
| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
| CA SUBSCRIBER PRICE | -1.02 | -78.69 |

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FILE 'HCAPLUS' ENTERED AT 15:17:20 ON 26 JUL 1999
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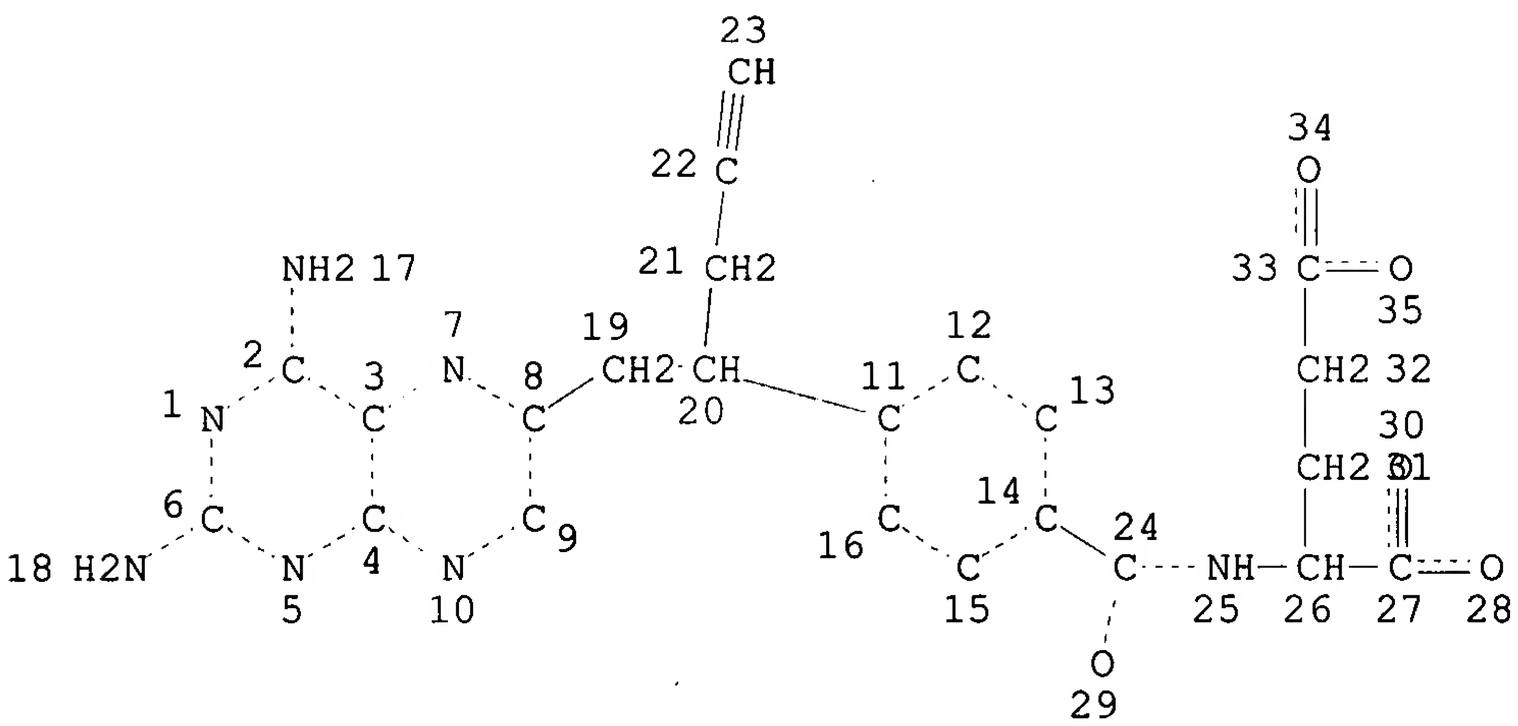
FILE 'BIOSIS' ENTERED AT 15:17:20 ON 26 JUL 1999


FILE 'EMBASE' ENTERED AT 15:17:20 ON 26 JUL 1999


FILE 'WPIDS' ENTERED AT 15:17:20 ON 26 JUL 1999

L6 STR



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STEREO ATTRIBUTES: NONE
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100.0% PROCESSED 21 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L8 ANSWER 1 OF 2 REGISTRY COPYRIGHT 1999 ACS
RN 146464-95-1 REGISTRY
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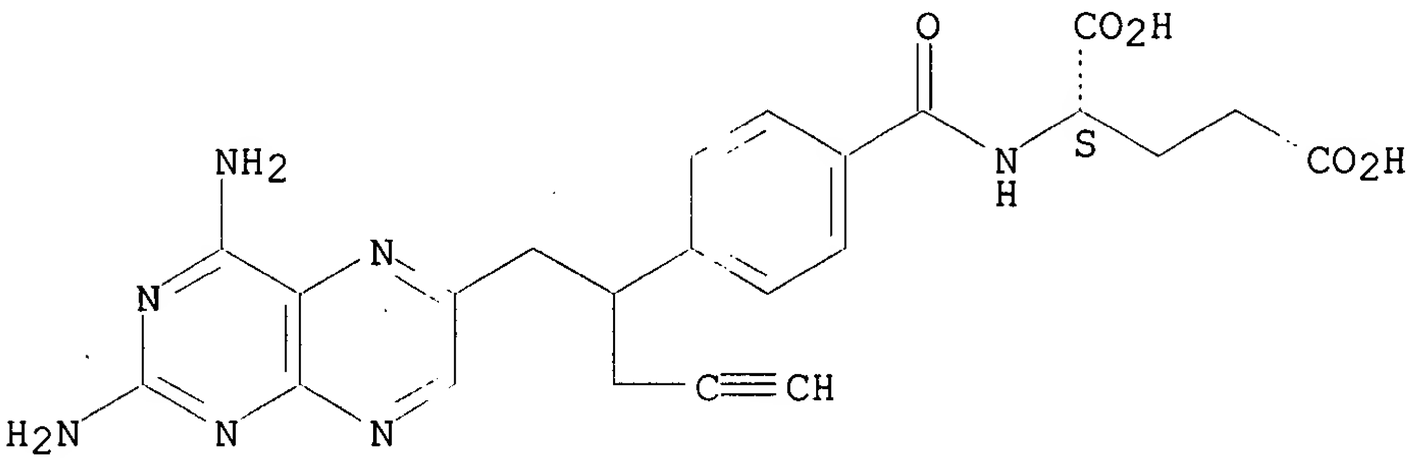
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)

3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:149573 Preparation and purified compositions of 10-propargyl-10-deazaaminopterin and methods of use in the treatment of tumors. Sirotnak, Frank M.; Piper, James R.; DeGraw, Joseph I.; Colwell, William T. (Sloan-Kettering Institute for Cancer Research, USA; SRI International; Sirotnak, Frank M.; Piper, James R.; DeGraw, Joseph I.; Colwell, William T.). PCT Int. Appl. WO 9802163 A1 19980122, 24 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US11982 19970716. PRIORITY: US 1996-21908 19960717.

AB Highly purified 10-propargyl-10-deazaaminopterin (10-propargyl-10dAM) compns., tested in xenograft models for their efficacy against human tumors, are shown to be far superior to methotrexate ("MTX") and are even superior to the newer clin. candidate edatrexate ("EDX"). Moreover, 10-propargyl-10dAM showed a surprising ability to cure tumors such that there was no evidence of tumor growth several weeks after the cessation of therapy. Thus, highly purified compns. contg. 10-propargyl-10dAM can be used to treat human tumors, particularly human mammary tumors and human lung cancer.

REFERENCE 2: 122:240437 Heteroaroyl 10-deazaamino-pterine compounds and use for rheumatoid arthritis and other proliferative diseases. Degraw, Joseph I.; Colwell, William T.; Sirotnak, Francis M.; Smith, R. Lane; Piper, James R. (SRI International, USA). U.S. US 5354751 A 19941011, 24 pp. Cont.-in-part of U.S. Ser. No. 28,431. (English). CODEN: USXXAM. APPLICATION: US 1993-90750 19930712. PRIORITY: US 1992-845407 19920303; US 1992-875779 19920429; US 1992-938105 19920831; US 1993-8919 19930126; US 1993-28431 19930309.

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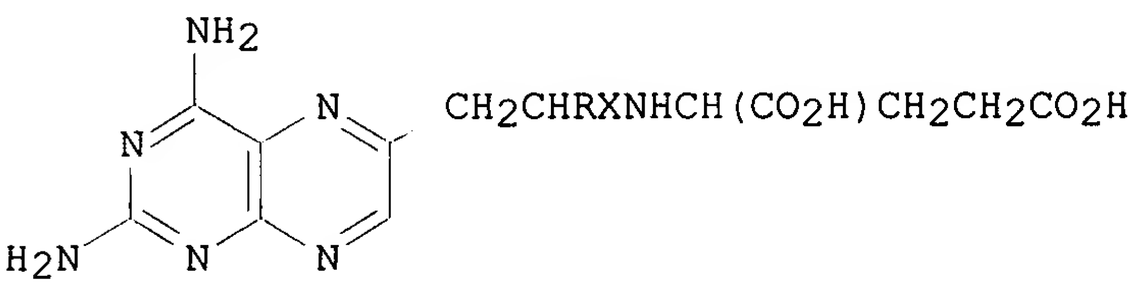


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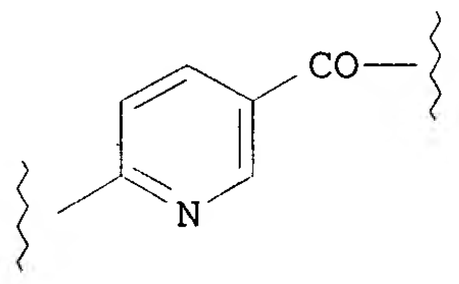


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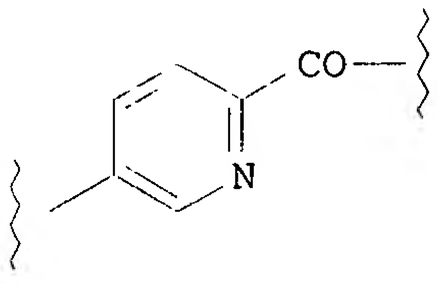


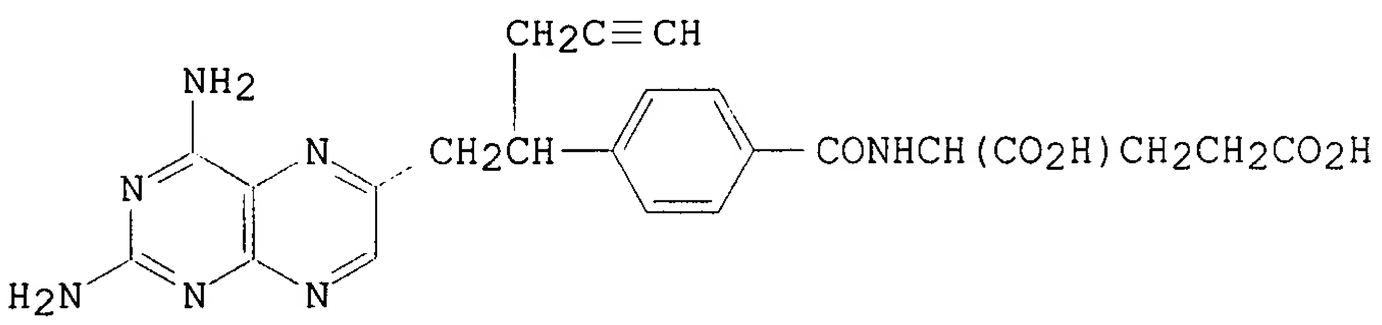

III

AB There is disclosed certain heteroaroyl 10-deazaaminopterin (I; X = one of II or III; R = H or alkyl, alkenyl, or alkynyl have from 1 to 8 C atoms) and 5,10- and 8,10-dideazaminopterin compds. and their use for treatment of rheumatoid arthritis and related diseases and preparative process. Also disclosed are 10-alkenyl(and alkynyl)-10-deazaminopterins for treatment of rheumatoid arthritis and for leukemia and ascites tumors and

preparative process. Antiarthritic activity in mice was assessed by visually obsd. presence of inflammation and caliper-measured degree of paw swelling: the no. of mice affected by disease was considerably decreased by administration of I (e.g., 4/8 affected, 2.19-2.35 paw thickness vs. 41/43 affected, 2.29-2.73 paw thickness for 10-allyl-10-deazaaminopterin at 12 mg/kg dose). Growth inhibition of leukemia cells (IC50 nM): 10-allyl-10-deazaaminopterin (4.30), 10-propargyl-10-deazaaminopterin (2.0). Antitumorigenic affect of 10-propargyl-10-deazaaminopterin: at 36 mg/kg, total suppression of growth of tumor at 14 and 21 day post-treatment points. Pharmaceutical formulations are given.

REFERENCE 3: 119:72415 Synthesis and antitumor activity of 10-propargyl-10-deazaaminopterin. DeGraw, Joseph I.; Colwell, William T.; Piper, James R.; Sirotnak, Francis M. (Bio-Org. Chem. Lab., SRI Int., Menlo Park, CA, 94025, USA). J. Med. Chem., 36(15), 2228-31 (English) 1993. CODEN: JMCMAR. ISSN: 0022-2623.

GI

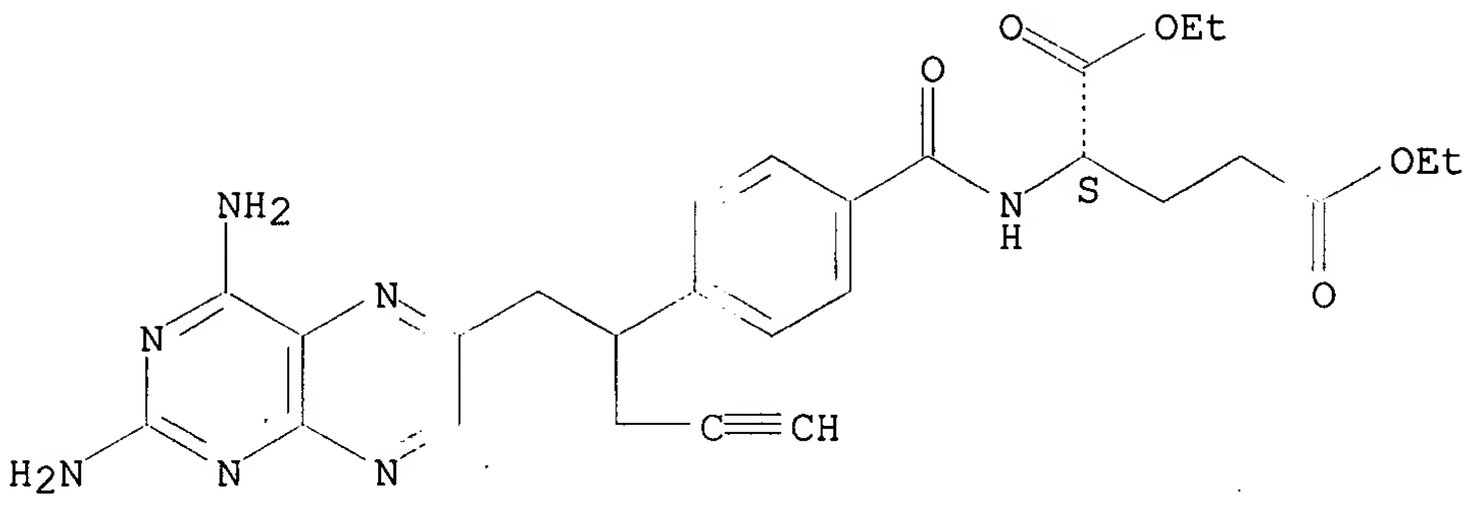


I

AB Successive alkylation of di-Me homoterephthalate with propargyl bromide and 2,4-diamino-6-(bromomethyl)pteridine followed by ester sapon. at room temp. afforded 2,4-diamino-4-deoxy-10-carboxy-10-propargyl-10-deazapteroic acid. The 10-COOH was readily decarboxylated by heating in DMSO at a temp. of only 120.degree.C to yield the diamino-10-propargyl-10-deazapteroic acid intermediated. Coupling with di-Et L-glutamate and ester hydrolysis gave the title compd. (I). The 10-propargyl analog was about 5 times more potent than MTX as an inhibitor of growth in L1210 cells, but was only one-third as potent as an inhibitor of DHFR from L1210. The analog was transported inward very effectively in L1210 cells showing a 10-fold advantage over MTX. At a dose of 36 mg/kg the 10-propargyl compd. caused shrinkage of the E0771 solid murine mammary tumor to only 1% of untreated controls.

L8 ANSWER 2 OF 2 REGISTRY COPYRIGHT 1999 ACS
RN 146464-94-0 REGISTRY
CN L-Glutamic acid, N-[4-[1-[(2,4-diamino-6-pteridinyl)methyl]-3-butynyl]benzoyl]-, diethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H31 N7 O5
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
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I.; Colwell, William T.; Sirotnak, Francis M.; Smith, R. Lane; Piper, James R. (SRI International, USA). U.S. US 5354751 A 19941011, 24 pp. Cont.-in-part of U.S. Ser. No. 28,431. (English). CODEN: USXXAM. APPLICATION: US 1993-90750 19930712. PRIORITY: US 1992-845407 19920303; US 1992-875779 19920429; US 1992-938105 19920831; US 1993-8919 19930126; US 1993-28431 19930309.

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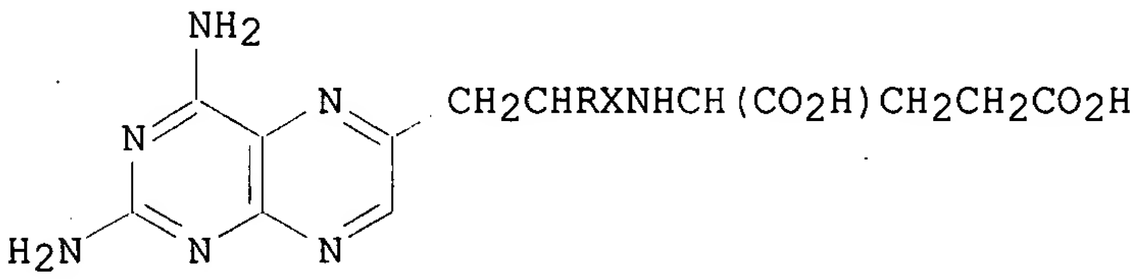

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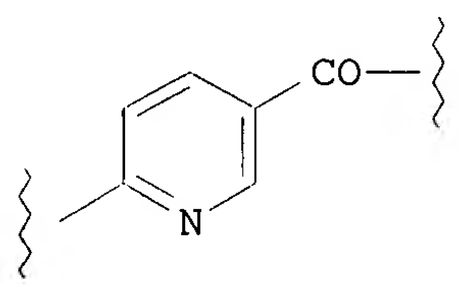

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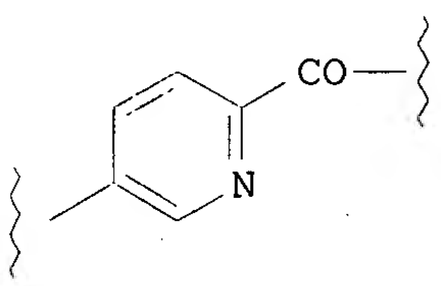

III

AB There is disclosed certain heteroaroyl 10-deazaaminopterin (I; X = one of II or III; R = H or alkyl, alkenyl, or alkynyl have from 1 to 8 C atoms) and 5,10- and 8,10-dideazaminopterin compds. and their use for treatment of rheumatoid arthritis and related diseases and preparative process. Also disclosed are 10-alkenyl(and alkynyl)-10-deazaminopterins for treatment of rheumatoid arthritis and for leukemia and ascites tumors and preparative process. Antiarthritic activity in mice was assessed by visually obsd. presence of inflammation and caliper-measured degree of paw
swelling: the no. of mice affected by disease was considerably decreased by administration of I (e.g., 4/8 affected, 2.19-2.35 paw thickness vs. 41/43 affected, 2.29-2.73 paw thickness for 10-allyl-10-deazaaminopterin at 12 mg/kg dose). Growth inhibition of leukemia cells (IC50 nM): 10-allyl-10-deazaaminopterin (4.30), 10-propargyl-10-deazaaminopterin

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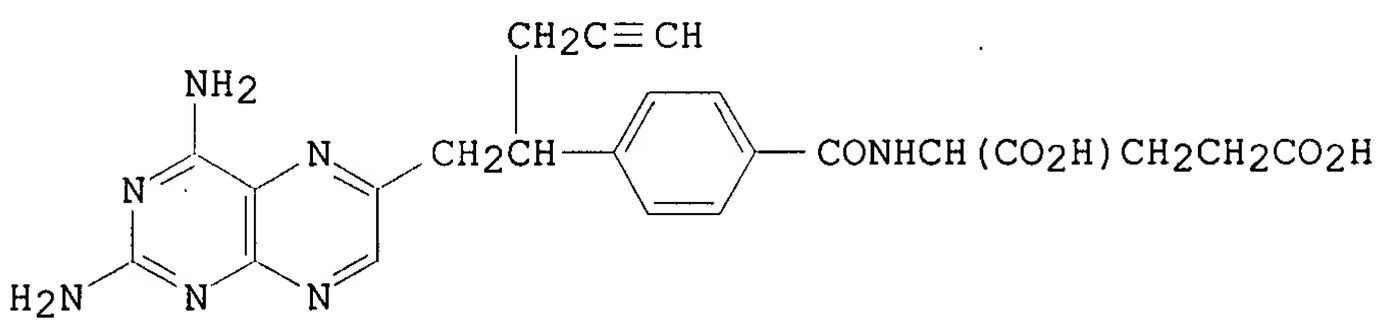

I

AB Successive alkylation of di-Me homoterephthalate with propargyl bromide and 2,4-diamino-6-(bromomethyl)pteridine followed by ester sapon. at room temp. afforded 2,4-diamino-4-deoxy-10-carboxy-10-propargyl-10-deazapteroic acid. The 10-COOH was readily decarboxylated by heating in DMSO at a temp. of only 120.degree.C to yield the diamino-10-propargyl-10-deazapteroic acid intermediated. Coupling with di-Et L-glutamate and ester hydrolysis gave the title compd. (I). The 10-propargyl analog was about 5 times more potent than MTX as an inhibitor of growth in L1210 cells, but was only one-third as potent as an inhibitor of DHFR from L1210. The analog was transported inward very effectively in L1210 cells showing a 10-fold advantage over MTX. At a dose of 36 mg/kg the 10-propargyl compd. caused shrinkage of the E0771 solid murine mammary tumor to only 1% of untreated controls.

```
=> e "10-propargyl-10-deaza-amino pterine"/cn

E1            1
10-PROPARGYL-10-CARBOMETHOXY-4-DEOXY-4-AMINO-10-DEAZAPTEROIC
                    ACID METHYL ESTER/CN
E2            1     10-PROPARGYL-10-CARBOXY-4-DEOXY-4-AMINO-10-DEAZAPTEROIC
ACID
                    /CN
E3            0 --> 10-PROPARGYL-10-DEAZA-AMINO PTERINE/CN
E4            1     10-PROPARGYL-4-DEOXY-4-AMINO-10-DEAZAPTEROIC ACID/CN
E5            1     10-PROPARGYL-5,8-DIDEAZAFOLIC ACID/CN
E6            1     10-PROPARGYL-5,8-DIDEAZAFOLIC ACID PENTAGLUTAMATE/CN
E7            1     10-PROPARGYL-5,8-DIDEAZAFOLIC ACID TETRAGLUTAMATE/CN
E8            1     10-PROPARGYLACRIDONE/CN
E9            1     10-PROPARGYLESTR-4-ENE-3,17-DIONE/CN
E10           1     10-PROPARGYLPHENOTHIAZINE/CN
E11           1     10-PROPIONYL-3,7-BIS(DIMETHYLAMINO)PHENOTHIAZINE/CN
E12           1     10-PROPIONYLDITHRANOL/CN

=> s propargyl(l)deaza(l)amino(l)pterine

          1435 PROPARGYL
           964 DEAZA
```

```
        2700742 AMINO
           7178 AMINOS
        2700742 AMINO
                   (AMINO OR AMINOS)
             20 PTERINE
L9            0 PROPARGYL(L)DEAZA(L)AMINO(L)PTERINE

=> s e4

L10           1 "10-PROPARGYL-4-DEOXY-4-AMINO-10-DEAZAPTEROIC ACID"/CN

=> d ide cbib


L10  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 1999 ACS
RN   146464-93-9  REGISTRY
CN   Benzoic acid, 4-[1-[(2,4-diamino-6-pteridinyl)methyl]-3-butynyl]- (9CI)
     (CA INDEX NAME)
OTHER NAMES:
CN   10-Propargyl-4-deoxy-4-amino-10-deazapteroic acid
FS   3D CONCORD
MF   C18 H16 N6 O2
SR   CA
LC   STN Files:   CA, CAPLUS, CASREACT, TOXLIT, USPATFULL
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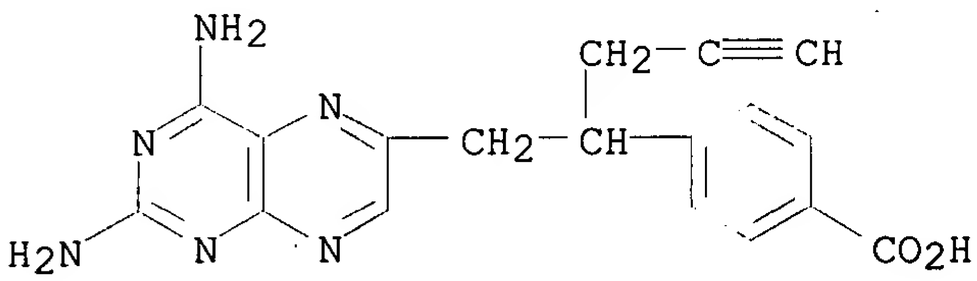


6 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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REFERENCE 2: 125:196375 Preparation of [[(diaminopyridopyrimidinyl)methylamino]benzoyl]glutamates and analogs as antiinflammatory and antineoplastic agents. Degraw, Joseph I.; Colwell, William T.; Sirotnak, Francis M.; Smith, R. Lane; Piper, James R. (Sri International, USA; Sloan-Kettering Institute). U.S. US 5536724 A 19960716, 31 pp. Cont.-in-part of U.S. 5,354,751. (English). CODEN: USXXAM. APPLICATION: US 1993-140793 19931021. PRIORITY: US 1992-845407 19920303; US 1992-875779 19920429; US 1992-938105 19920831; US 1993-8919 19930126; US 1993-28431 19930309; US 1993-90750 19930712.

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